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PATENT ADMINISTRATOR
KATTEN MUCHIN ROSENMAN LLP
1025 THOMAS JEFFERSON STREET, N.W.
EAST LOBBY: SUITE 700
WASHINGTON, DC 20007-5201

| EXAMINER | |
|---|---|
| GRAFFEO, MICHEL | |
| **ART UNIT** | **PAPER NUMBER** |
| 1614 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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| 3 MONTHS | 01/30/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/669,251 | SHAPIRO, LELAND | |
| | Examiner | Art Unit | |
| | Michel Graffeo | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Action*

Claims 25-30 are examined.

Applicant has amended claim 25 and provided arguments for the patentability of claims 25-30 in the response filed 17 August 2006.

Applicant's arguments, see response, filed 17 August 2006, have been fully considered and are persuasive to the extent that the rejections under 35 USC §102 and §103, have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made. Any rejection not specifically stated in this Office Action has been withdrawn.

### *Double Patenting*

Applicant's request that the Double Patenting rejection over 10427929 be held in abeyance until it is made permanent is noted but will be maintained in this Office Action and future Office Actions until an appropriate terminal disclaimer is filed and approved.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-30 are rejected under 35 U.S.C. 112, first paragraph, because while the prior art teaches the use of prolinamide compounds to treat ischemia reperfusion with thrombolytic agents and free radical scavengers, the specification does not reasonably provide enablement for treating ischemia reperfusion injury with alpha1-antitrypsin, alpha1-antitrypsin-like agents, antielastase or antiproteinase-3 agens; the additional administration of a thrombolytic agent, and the additional use of a mechanical device to reestablish blood flow. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per factors indicated in the decision In re Wands, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation.

The factors include:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice that instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to a method of treating ischemia reperfusion injury, comprising administering at least one of α1-antitrypsin, α1-antitrypsin-like agent, antielastase, or antiproteinase-3 agent, a specific prolinamide or a combination thereof; additionally comprising administering a thrombolytic agent, a free radical scavenger and additionally comprising using a mechanical device to reestablish blood flow.

The relative skill of those in the art is generally that of a Ph.D. or M.D.

The present invention is unpredictable unless experimentation is shown for the treat of ischemia reperfusion injury with all the compounds of claim 1, along with all thrombolytic agents, and all mechanical device for reestablishing blood flow

The breadth of the claims

The claims are inclusive to all α1-antitrypsins, α1-antitrypsin-like agents, antielastase, or antiproteinase-3 agents, or combinations thereof; all thrombolytic agents and all mechanical devices for reestablishing blood flow.

The amount of direction or guidance provided and the presence or absence of working examples

The working examples are limited to the administration of (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl-2-(S)-methylpropyl]-

L-prolinamide to treat septic shock (Example 6.7), combined with γ-IFN (Example 6.8), to treating induced inflammation (Example 6.9) and combined with α1-antitrypsin to treat endotoxemia (Example 6.10).

No working examples showing α1-antitrypsins, α1-antitrypsin-like agents, antielastase, or antiproteinase-3 agents or (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl-2-(S)-methylpropyl]-L-prolinamide to treat ischemia reperfusion injury.

No working examples showings the addition of a thrombolytic agent of claim 26, or the using of a mechanical device for reestablishing blood flow of claims 27 and 30.

The quantity of experimentation necessary

Applicants have failed to provide guidance as to how the other compounds of claim 1 are effective in treating ischemia reperfusion injury or how (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl-2-(S)-methylpropyl]-L-prolinamide can treat ischemia reperfusion injury; or combined with a thrombolytic agent and a mechanical device for reestablishing blood flow. Therefore, undue experimentation would be required to practice the invention as it is claimed in its current scope.

Claims 25-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant has not conveyed possession of the invention with reasonable clarity to one skilled in the art. In particular, Applicant has not provided a description of the structure of a representative number of compounds which Applicant contends are alpha1-antitrypsin compounds, alpha1-antitrypsin-like agents, antielastase or antiproteinase-3 agents nor a description of the chemical and/or physical characteristics of a representative number of such compounds nor a description of how to obtain a representative number of said specific compounds.

To satisfy the written description requirement, applicant must convey with reasonable clarity to one skilled in the art, as of the filing date that application was in possession of the claimed invention. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

***Response to Arguments - 35 USC § 112***

Applicant's arguments filed 17 August 2006 have been fully considered but they are not persuasive. Applicant argues that the Specification supports a method of treating ischemia reperfusion injury on page 22 because it teaches that that a reduction in inflammation can treat ischemia reperfusion injury. Such statement without more is a tantamount to a hypothesis. A suggestion in the Specification that a reduction in inflammation can treat ischemia reperfusion injury is insufficient without any reasonable links or a showing between the reduction in inflammation and a treatment of ischemia reperfusion injury.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 25 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gyorkos et al. (5,618,792) in view of Szabo et al. Peroxynitrite-mediated oxidation of dihydrorhodamine 123 occurs in early stages of endotoxic and hemorrhagic shock and ischemia-reperfusion injury FEBS Letters 372 (1995) 229-232 and further in view of US Patent Application Publication No. 2004/0132666 to Neuwelt et al.

Gyorkos et al. teach substituted oxadiazole, thiadiazole and triazole peptoids, which are useful as inhibitors of serine proteases including human neutrophil elastase (elastase inhibitory activity). Note the examples I-XVI are the same compounds of disclosed in applicants' claim 1. Note particularly column 7, lines 58-67 and column 8, lines 1-67 teaches the instant compounds are formulated into pharmaceutical compositions. Column 7, lines 45-57 teaches the instant compounds are used to treat various diseases such as myocardial ischemia/reperfusion or other conditions disclosed in column 1, lines 28-42.

The instant invention differs from the cited references in that the cited reference does not teach the administration of a free radical scavenger such as dihydrorhodamine. Szabo et al. teach the administration of dihydrorhodamine in vivo to rats which have induced splanchnic ischemia and reperfusion (see material and methods on page 229) and further teach that peroxynitrite, a potent and reactive oxidant, is formed during ischemia and reperfusion (see also page 229 Introduction) as well as that the early formation of peroxynitrite necessitates the introduction of different therapeutic strategies (see page 232).

One of ordinary skill in the art would have been motivated to combine the above references and as combined teach the claimed invention as claimed. One of ordinary skill in the art would have been motivated to combine the references because all are directed to the treatment of ischemia and/or reperfusion. Further, Szabo et al. teach that peroxynitrite, a reactive oxidant, resulting from ischemia-reperfusion (see Introduction) has cytotoxic actions but that scavengers such as dihydrorhodamine react

with peroxynitrite (see page 232). Finally, Neuwelt et al. teach the treatment of ischemia-reperfusion with free radical scavengers (see Title and Abstract). Clearly, one skilled in the art would have assumed the combination of the individual agents known to treat ischemia reperfusion injuries into a single composition would give an additive effect in the absence of evidence to the contrary.

Claims 25-26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gyorkos et al. (5,618,792), Szabo et al. and Neuwelt et al. as applied to claims 25 and 28 above in view of Verstraete, "Intravenous administration of a thrombolytic agent is the only realistic therapeutic approach in evolving myocardial infarction", European Heart Journal, Vol. 6, pp. 586-593 (1985).

The instant invention differs from the cited reference in that the cited reference does not teach the addition of a second agent, a thrombolytic agent as disclosed in claim 26. However, the secondary reference, Verstraete, teaches a thrombolytic agent such as streptokinase to treat myocardial infarction, an ischemia reperfusion injury. Clearly, one skilled in the art would have assumed the combination of two individual agents know to treat ischemia reperfusion injuries into a single composition would give an additive effect in the absence of evidence to the contrary.

One of ordinary skill in the art would have been motivated to combine the above references and as combined teach the claimed invention as claimed. One of ordinary skill in the art would have been motivated to combine the references because all are directed to the treatment of ischemia and/or reperfusion. Further, Szabo et al. teach

that peroxynitrite, a reactive oxidant, resulting from ischemia-reperfusion (see Introduction) has cytotoxic actions but that scavengers such as dihydrorhodamine react with peroxynitrite (see page 232). As noted above, the secondary reference, Verstraete, teaches a thrombolytic agent such as streptokinase to treat myocardial infarction, an ischemia reperfusion injury. Clearly, one skilled in the art would have assumed the combination of two individual agents know to treat ischemia reperfusion injuries into a single composition would give an additive effect in the absence of evidence to the contrary. Moreover, combining agents which are known to be useful for the treatment of ischemia and reperfusion individually into a singe composition useful for the very same purpose is prima facie obvious. See In re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining the claimed agents flows logically from their having been individually taught in the prior art. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

Claims 25-28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gyorkos et al. (5,618,792), Szabo et al. Peroxynitrite-mediated oxidation of dihydrorhodamine 123 occurs in early stages of endotoxic and hemorrhagic shock and ischemia-reperfusion injury FEBS Letters 372 (1995) 229-232 and Neuwelt et al. as applied to claims 25 and 28 above and further in view of Woods (5,180,366).

The instant invention differs from the cited references in that the cited references do not teach the additional use of a mechanical device for reestablishing blood flow. However, the tertiary reference, Woods, teaches an apparatus used to reestablish blood flow in a patient that involves angioplasty. Clearly, the use of mechanical devices that involves angioplasty is well-known in the art.

One of ordinary skill in the art would have been motivated to combine the above references and as combined teach the claimed invention as claimed. One of ordinary skill in the art would have been motivated to combine the references because all are directed to the treatment of ischemia and/or reperfusion. Combining agents which are known to be useful for the treatment of ischemia and reperfusion individually into a singe composition useful for the very same purpose is prima facie obvious. See In re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two therapies each of which is taught by the prior art to be useful for the same purpose, in order to form a third product to be used for the very same purpose, the idea of combining the claimed agents with a device flows logically from their having been individually taught in the prior art. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

## ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michel Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

16 January 2007
MG

Ardin H. Marschel 1/21/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER